ethnological aspects, but also as it pertains to the theory of development of one of the most frequent deformities of all civilized people.

	Adult negro.	*Adult white.*	*Negro children.*
Number of feet examined	88	34	40
Percentage of flat feet	56.8	5.8	25
Hallux valgus without flat foot	27.0 per ct.	35.0 per ct.	5 per ct.
Without flat foot or hallux valgus	16.2 "	59.2 "	75 "
Hallux valgus present in	79.5 "	41.0 "	25 "
Of flat feet hallux valgus present in	92.0 "	100.0 "	80 "

STUDIES ON THE ANTAGONISTIC ACTION OF DRUGS.

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WITH AN INTRODUCTION BY TORALD SOLLMAN, M.D.

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I. Introduction.

The question whether a drug which excites a given structure can remove the effects of another drug which depresses the same structure cannot be considered as answered. Recent evidence—as the work of J. C. Rothberger[1] on the antagonism of physostigmine and curare, and that of A. P. Mathews[2] on atropine and pilocarpine, and that of Stokvis[3] on digitalin and quinine—favors this view, without being entirely decisive. Accepting the theoretical possibility that an excitant can remove the symptoms produced by a depressant, there still remains the question whether the excitant really removes the depression or whether it only masks it through the excitation. It would seem, *a priori*, that the former can only be the case when the excitant prevents the depressant from combining with the protoplasm, as, for instance, when an alkali prevents the action of an acid. In these cases the antagonism is chemical or physical. If, however, both the depressant and the excitant combine with the protoplasm, as is supposed to be the case when, for example, pilocarpine and atropine act simultaneously, it must be assumed that they both produce their action. If in this case no noticeable phenomena result, this is not because the drugs exert no action, but because the resultant of the actions is zero. For example, it is quite easily conceivable that a cell depressed through starvation may be restored temporarily to its original activity, say by an increase of temperature, and may for a time behave like a normal cell. Nevertheless, it is far from normal; it will probably show chemical, functional, and structural changes, and will, for instance, fatigue more readily. Similarly, if we assume that the biogen-pilocarpine compound functionates very actively, the biogen-atropine compound very sluggishly, then the biogen$\genfrac{}{}{0pt}{}{\diagup\text{atropine}}{\diagdown\text{pilocarpine}}$ compound may functionate very nearly like the free biogen molecule. Nevertheless, a chemical difference must exist between the compound and the free biogen molecule, and this difference must entail other differences in the chemistry, functions, or morphology of the cell. The discovery of such differences in cases in which a complete physiological antagonism is assumed would go far to support this thesis.

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[1] Pflüger's Archiv, 1901, Bd. lxxxvii. p. 117.

[2] American Journal of Physiology, vol. vi. p. 207.

[3] Virchow's Festschrift, 1891, Bd. iii. p. 349.

Dr. Haskins, at my suggestion, undertook the investigation of some such phenomena, the results of his work being detailed in the following papers:

The histological changes which alcohol is believed to produce in nerve cells seemed to offer a fit object for this study, the question being, Whether a drug which lessens the toxic effects of alcohol also lessens the histological lesions. Since strychnine is credited with counteracting the physiological effects of alcohol, it was chosen as an antidote. It may be said at once that the results throw no light upon the question: first, because the alcohol did not produce the lesions which are credited to it; and, secondly, because strychnine did not prove to be very efficient in preventing the alcohol symptoms. The data seem of sufficient practical interest in other directions to merit reporting.

It was then planned to investigate the subject along an entirely different line, by studying the effect of the simultaneous action of stimulants and depressants on yeast cultures. As no reliable stimulant could be found among drugs, various degrees of heat were resorted to, and were contrasted with the depressant action of strychnine. The results show that the antagonism is far from being as simple a phenomenon as one would expect if the stimulant action of heat neutralized the depressant effect of strychnine. They are more in agreement with the complicated condition which would obtain if the stimulation and depression were superimposed. It must be granted that the stimulation by heat may be of quite a different nature from stimulation by drugs. It must also be granted that there may be various types of physiological antagonism among drugs. These are matters which cannot be considered as definitely settled until a large number of antagonisms have been studied in detail.

II. The Effect of Strychnine on Alcohol Poisoning.

Experiment 1. Summary. Two guinea pigs were each given 40 c.c. of 40 per cent. alcohol per kilo body-weight by intraperitoneal injection, divided into seven doses, during a period of twelve hours. This sufficed to kill one of them. The surviving guinea-pig had been given in addition to the alcohol 0.15 mg. of strychnine sulphate per kilo weight subcutaneously in a 1 : 20,000 solution, also divided into seven doses.

Protocol. Two healthy guinea-pigs were selected—A, weighing 290 gm.; B, 350 gm. 8 A.M., 10 c.c. of 40 per cent. alcohol per kilo weight injected into A and B; also 0.1 mg. of strychnine sulphate per kilo weight into B. Ten minutes later B lies in a stupor and has rhythmical tremors of the legs. One hour after injection, B the same; A has shown little effect from the alcohol aside from restlessness and occasional shivering; respiration of A, 65; of B, 85 per minute. Two hours after injection A has almost recovered from his indisposition, while B has but partially recovered.

10 A.M., the second injection: A and B are given 5 c.c. of 40 per cent. alcohol per kilo weight; B also 0.025 mg. of strychnine sulphate per kilo weight. Five minutes later A has become indisposed, B lies in complete stupor, and exhibits the same tremors. During the next hour A gradually becomes partly paralyzed so that he cannot stand nor walk; B remains the same as before. Respiration of A keeps at about 60, of B at 70 per minute. Finally A lies over onto his side in a stupor, and has tremors of exactly the same rhythm as B. Four and one-half hours after the injection both have recovered considerably, but A is more relaxed and indisposed than B.

2.30 P.M., the third injection: A and B receive 5 c.c. of 40 per cent. alcohol per kilo weight; B also receives 0.0125 mg. of strychnine sulphate per kilo weight. A becomes narcotized much more quickly than B. Fifteen minutes after injection both present the same symptoms as after the previous injection, namely, stupor and tremors. Respiration of A is 40, of B 80 per minute. Two and one-half hours after injection they are in the same condition.

5 P.M., the fourth injection of the same dosage as the third. Within a few minutes A ceases to have tremors and begins breathing by gasps. One and one-half hours after injection A seems to be paralyzed completely as far as voluntary muscles are concerned, since he lies relaxed and motionless. Respiration of A is 28, of B 65 per minute. B lies in the same condition as before.

7 P.M., the fifth injection: A and B receive 5 c.c. of 40 per cent. alcohol per kilo weight. No more strychnine is given.

7.20 P.M., the sixth injection, same as fifth.

7.30 P.M., the seventh injection, same as fifth and sixth. Respiration of A is 10, of B 17 per minute. A is evidently almost dead. B is weaker, but has the leg movements still.

8 P.M., A is dead; B is alive and not fully paralyzed. B is killed. Both animals are dissected and portions of the central nervous system removed for histological examination.

Experiment 2. Summary. Two cats were each given intraperitoneally 20 c.c. of 40 per cent. alcohol per kilo body-weight in two doses of 10 c.c., five and one-half hours apart. One cat received in addition 0.1 mg. per kilo weight of strychnine sulphate in 1 : 20,000 solution subcutaneously in three doses. The latter died during the night. The other cat died forty-six and one-half hours after the first injection.

Protocol. Two cats were taken, Cat 1 weighing 2980 gm., Cat 2 2180 gm. Cat 2 was not perfectly healthy, as evidenced by a discharge from the eyes.

9 A.M., Cat 1, pulse 100, respiration 40. Cat 2, pulse 108, respiration 48.

9.30 A.M., first injection intraperitoneally into Cat 1 and Cat 2 of 10 c.c. of 40 per cent. alcohol per kilo weight and 0.025 mg. of strychnine sulphate per kilo weight subcutaneously into Cat 2. Seven minutes later Cat 1 shows beginning narcosis. Thirteen minutes are required to make Cat 2 lie down quietly. Fifty minutes after the injection, pulse of Cat 1 is 96, of Cat 2 is 100 per minute; both are completely paralyzed in the hind legs. One and one-half hours after injection both lie quietly sleeping, Cat 1, pulse 100, respiration 80; Cat 2, pulse 120, respiration 45. Two hours after injection Cat 2 receives another dose of strychnine of the same size as before. Two and one-half hours after first injection, Cat 1, pulse 120, respiration 68; Cat 2, pulse 120, respiration 36. Five hours after injection Cat 1 shows partial recovery. Cat 1, pulse 120, respiration 52; Cat 2, pulse 120; respiration 36.

3 P.M., second injection into Cat 1 and Cat 2 of 10 c.c. of 40 per cent. alcohol per kilo weight and of 0.05 mg. of strychnine sulphate into Cat 2. Both lie relaxed within a few minutes. Fifteen minutes after injection, Cat 1, pulse 120, respiration 72; Cat 2, pulse 120, respiration 48. One and one-quarter hours after injection both lying unconscious still. Cat 1, pulse 120, respiration 68; Cat 2, pulse 120, respiration 32. One-quarter of an hour later Cat 2 begins to gasp, and respiration stops within a few minutes, then begins again at the rate of 16 per minute.

Cat 2 died during the night.

Cat 1 lay unconscious all the next day, but could be aroused somewhat; the respiration varied from 44 at 8 A.M., 26 at 2.30 P.M., to 34 at 4.30 P.M. At 7.30 the next morning he was breathing feebly. Cat 1 died at 8 A.M.

Experiment 3. Summary. Two cats were each given 20 c.c. of 40 per cent. alcohol per kilo body-weight intraperitoneally in two equal doses, twenty-four hours apart. One died twenty-six and three-quarter hours after the first injection. The survivor had received 0.15 mg. of strychnine sulphate per kilo body-weight in six doses.

Protocol. Two healthy cats were taken, Cat 1 weighing 2700 gm., Cat 2, 2610 gm.

9 A.M., Cat 1, pulse 140, respiration 36; Cat 2, pulse 140, respiration 42. First injection: Cat 1 and Cat 2 receive 10 c.c. of 40 per cent. alcohol per kilo weight intraperitoneally; Cat 2 gets 0.025 mg. of strychnine sulphate solution 1 : 20,000 subcutaneously. Four minutes after injection both are lying on the side. Twelve minutes after injection, Cat 1, pulse 140, respiration 78; Cat 2, pulse 140, respiration 78. Forty-five minutes after injection, Cat 1, pulse 140, respiration 92; Cat 2, pulse 140, respiration 120. One hour after injection Cat 2 is given another dose of strychnine of the same size. Both make movements occasionally. One and one-half hours after first injection, Cat 1, pulse 140, respiration 64; Cat 2, pulse 140, respiration 80; both are sleepy. Two and one-quarter hours after injection, gave the third dose of strychnine to Cat 2. Two and one-half hours after first injection both appear exactly as if merely asleep. Cat 1, pulse 140, respiration 64; Cat 2, pulse 140, respiration 56. Five hours after injection both asleep. Cat 1, pulse 140, respiration 46; Cat 2, pulse

140, respiration 36. Fifteen minutes later another dose of strychnine to Cat 2. Five and three-quarter hours after first injection Cat 1 moves about, using the front legs, the hind legs still being useless. Cat 1, respiration 44; Cat 2, respiration 40. Six and one-half hours after injection another dose of strychnine to Cat 2. Forty-five minutes later, Cat 1, pulse 120, respiration 40; Cat 2, pulse 120, respiration 28. Cat 1 is more conscious and more desirous of moving about than Cat 2. The next morning both were alive and conscious. Cat 2 seems to be more vigorous than Cat 1, for he will walk about.

9 A.M., Cat 1, pulse 140, respiration 28; Cat 2, pulse 140, respiration 36. Second injection the same as the first. Twenty minutes later both lie quiet. Cat 1, pulse 140, respiration 28; Cat 2, pulse 140, respiration 80. One hour after injection, Cat 1, pulse 142, respiration 42; Cat 2, pulse 140, respiration 44; Cat 2 more conscious than Cat 1. Two and one-quarter hours after injection Cat 1 begins to gasp. Five minutes later Cat 1 dies; Cat 2 is asleep, pulse 140, respiration 28. Allowed Cat 2 to live one and one-quarter hours longer; pulse and respiration remained unchanged; made voluntary movements and reacted to pain.

Experiment 4. Summary. The effect of strychnine in counteracting alcohol when given in smaller doses during a longer period was tested in this experiment. Two kittens were each given 35 c.c. of 20 per cent. alcohol and 105 c.c. of 40 per cent. alcohol per kilo body-weight during thirteen days, and one of them received 3.1 mg. of strychnine sulphate per kilo weight in 1 : 5000 solution in addition to alcohol. Neither cat died. The cat that received strychnine showed a somewhat greater paralytic effect at the end of the experiment.

Protocol. Two healthy and lively kittens were taken, Cat 1 weighing 930 gm., Cat, 2 910 gm.

First day, 12.45 P.M., subcutaneous injection of 0.1 mg. per kilo weight of strychnine sulphate into Cat 2. Twenty-five minutes later noticed increased reflex excitability, for Cat 2 would start up as if struck at every sudden sound.

2 P.M., injected 5 c.c. of 20 per cent. alcohol per kilo weight subcutaneously into Cat 1 and Cat 2. Twenty-five minutes after injection both are lying down, sleeping lightly. Cat 1, respiration 28; Cat 2, respiration 19; Cat 2 still excitable.

3 P.M., another injection of alcohol, same as before, and a second dose of strychnine to Cat 2. Excitability of Cat 2 has decreased. Thirty minutes after injection excitability of Cat 2 is again increased; both asleep; respiration of Cat 1 is 30, of Cat 2, 23.

4 P.M., neither seem to be under the influence of the alcohol.

Second day, 9 A.M., both are normal; eat and drink heartily. Cat 2 shows no increased reflex excitability.

9.30 A.M., injection of 5 c.c. of 20 per cent. alcohol per kilo weight subcutaneously into Cat 1 and Cat 2, and of 0.1 mg. of strychnine sulphate per kilo weight into Cat 2. Thirty minutes later neither show any alcohol effect. Cat 2 begins to manifest increase of excitability; respiration of each is 36 to 40.

10 A.M., second injection same as first. Thirty minutes later both are less lively, Cat 2 more restless than Cat 1.

11 A.M., third injection, same as before. Fifteen minutes later both are sleepy. Twenty-five minutes after the injection neither cares to

move about; respiration of each 40 to 48. When roused up Cat 1 shows weakness of the hind legs; Cat 2 does not. Four hours after injection both have almost recovered.

3.30 P.M., fourth injection, same as before. One hour after injection both are sleepy, but can walk naturally when aroused; Cat 2 still shows increase of excitability.

Third day, 8.30 A.M., both seem normal; eat and drink freely.

8.40 A.M., first injection, same as on the day before. Thirty minutes later no effect noticeable.

9.20 A.M., second injection, 5 c.c. of 40 per cent. alcohol per kilo weight, subcutaneously into Cat 1 and Cat 2 and 0.1 mg. of strychnine sulphate per kilo weight into Cat 2. Forty minutes later both are asleep.

10.40 A.M., third injection, same as second. Cat 2 becomes very restless within a few minutes. Thirty minutes after injection both lie quietly; Cat 2 is more excitable than he has been. Forty-five minutes after injection both are disposed to lie still, but can walk with a wobbling gait when aroused. Three and one-half hours after injection both are sleepy; respiration 34 to 36; both show partial paralysis of the hind legs, tending to stagger and fall over onto the hip in walking. Thirty minutes later an extra dose of strychnine to Cat 2.

4 P.M., both are asleep; can walk better; Cat 2 is slightly excitable.

Fourth and fifth days: No drugs were administered.

Sixth day: Kittens are normal.

9.40 A.M., injection of 0.1 mg. of strychnine sulphate per kilo weight into Cat 2.

10.12 A.M., injection of 5 c.c. of 40 per cent. alcohol per kilo weight into Cat 1 and Cat 2.

10.55 A.M., second injection of alcohol and strychnine in the same doses as before. Twenty minutes later both are lying down. Four and one-half hours after injection Cat 1 seems to be sleepier than Cat 2; Cat 2 is less excitable than usual.

3.30 P.M., injection of an extra dose of strychnine into Cat 2. Twenty minutes later Cat 2 shows increased excitability.

4 P.M., third injection, same as second. Fifteen minutes later both stagger when they walk.

Seventh day: No drugs given. Eighth day: Both seem normal; have good appetite.

2.15 P.M., injection of 10 c.c. of 40 per cent. alcohol per kilo weight into Cat 1 and Cat 2, and of 0.2 mg. of strychnine sulphate per kilo weight into Cat 2. Twenty minutes later both are sleepy; Cat 2 is not excitable.

3.30 P.M., second injection, 5 c.c. of 40 per cent. alcohol per kilo weight, into Cat 1 and Cat 2; 0.2 mg. of strychnine sulphate per kilo weight into Cat 2. Thirty minutes later both are lying quietly; both stagger when made to walk; Cat 2 walks steadier than Cat 1.

Ninth day: Neither is lively; can walk, but is indisposed to. Cat 2 seems sicker than Cat 1.

9 A.M., injection of 10 c.c. of 40 per cent. alcohol per kilo weight, subcutaneously into Cat 1 and Cat 2, and of 0.2 mg. of strychnine sulphate per kilo weight into Cat 2. Twenty-five minutes later both are lying down asleep. Two and one-quarter hours after injection both can walk about; neither would eat much meat.

11.15 A.M., second injection, 5 c.c. of 40 per cent. alcohol per kilo weight, into Cat 1 and Cat 2; 0.1 mg. of strychnine sulphate into Cat 2. Three and one-quarter hours later neither can walk well; Cat 1 is steadier than Cat 2; Cat 2 is very sleepy and shows no increase of reflex excitability.

3.20 P.M., extra dose of strychnine to Cat 2. Twenty minutes later Cat 2 shows slight excitability.

4.35 P.M., third injection, same as second.

Tenth day: Cat 2 is more indisposed than Cat 1. They have eaten the meat left in the cage the evening before.

9.20 A.M., injection of 10 c.c. of 40 per cent. alcohol per kilo weight into Cat 1 and Cat 2, and of 0.2 mg. of strychnine sulphate per kilo weight into Cat 2. Reweighed them: Cat 1 weighs 1060 gm., Cat 2 960 gm., Cat 1 having gained 130 gm. and Cat 2, 50 gm. in eight days. One and one-half hours later Cat 2 is more profoundly asleep than Cat 1; respiration of Cat 1 is 36, of Cat 2, 22.

3 P.M., second injection, 5 c.c. of 40 per cent. alcohol per kilo weight, into Cat 1 and Cat 2; 0.1 mg. of strychnine sulphate per kilo weight into Cat 2. Twenty minutes later Cat 1 walks unsteadily; Cat 2 cannot walk.

Eleventh day: No drugs given. Twelfth day: Both seem to have recovered; Cat 1 is livelier than Cat 2.

11.25 A.M., injection of 10 c.c. of 40 per cent. alcohol per kilo weight into Cat 1 and Cat 2, and of 0.2 mg. of strychnine sulphate per kilo weight into Cat 2. Two and one-half hours after injection they have recovered partially from the alcohol.

2.15 P.M., second injection, 5 c.c. of 40 per cent. alcohol per kilo weight, into Cat 1 and Cat 2; 0.1 mg. of strychnine sulphate into Cat 2. One hour later Cat 2 is soundest asleep and weakest when it tries to walk.

3.30 P.M., third injection, 10 c.c. of 40 per cent. alcohol per kilo weight, into Cat 1 and Cat 2; 0.1 mg. of strychnine sulphate into Cat 2. Forty minutes later both show the most marked paralytic effect yet obtained. Cat 1 can only crawl a little when aroused; Cat 2 lies perfectly relaxed and cannot be made to move.

Thirteenth day: 9.30 A.M., both cats are still narcotized. Cat 2 is still paralyzed, more than Cat 1. Respiration of Cat 1 is 19, of Cat 2 12. Weight of Cat 1 is 1060 gm., of Cat 2 is 910 gm., Cat 1 being of the same weight as on the ninth day, Cat 2 being 50 gm. lighter.

10.30 A.M., intraperitoneal injection of 5 c.c. of 40 per cent. alcohol per kilo weight into Cat 1 and Cat 2; 0.1 mg. of strychnine sulphate per kilo weight into Cat 2. Neither gave evidence of pain from this injection.

3.15 P.M., Cat 1, pulse 130, respiration 28; Cat 2, pulse 130, respiration 20. Both are almost comatose.

3.30 P.M., killed both kittens.

III. DOES ACUTE AND SUBACUTE ALCOHOL POISONING LEAD TO HISTOLOGICAL CHANGES IN NERVE CELLS?

Method of Investigation. Pieces of the spinal cord, cerebellum, and cerebrum from corresponding locations were removed from guinea-pigs A and B of Experiment 1, and also from a normal guinea-pig. They were then fixed and hardened in absolute alcohol; sections were cut without embedding, and stained by Nissl's method on the same slides, as directed by C. C. Stewart.[1]

The same course was pursued with Cat 1 of Experiment 2 and Cats 1 and 2 of Experiment 3; also a normal cat. The tissues taken from the two kittens of Experiment 4 were fixed in 10 per cent. formalin, then put through graded alcohols and embedded in celloidin. The sections were stained with erythrosin, then with Nissl's methylene blue, as directed by F. R. Bailey.[2]

Results. The nerve cells of normal and drugged animals were not distinguishable the one from the other; all stained beautifully and showed no injury to nucleus or nucleolus. In all the sections the Nissl bodies or granulations of the large nerve cells were distinct and numerous. Only in extra thin portions of the sections were these granulations less numerous. No constant difference was observable between nerve cells from the normal and from the poisoned animals. It was, therefore, impossible to corroborate the results reported by C. C. Stewart.

IV. The Influence of Certain Drugs upon the Quantity of Gas Formed by Yeast.

Method of Experimentation. Fermentation tubes were used, the amount of gas formed from a given amount of glucose solution by the action of yeast within a given time being estimated. The ordinary method was found to be too unreliable, and it was modified as follows: The upright limb of the fermentation tube was filled about half-full with mercury, then, while the tube was still held inverted, a measured quantity (usually 2 c.c.) of a 5 per cent. solution of pure glucose in distilled water was run in on top of the mercury by means of a pipette, and was followed by an equal quantity of yeast mixture (usually 10 per cent. of compressed yeast suspended in distilled water), then the tube was immediately placed upright and all of the glucose-yeast mixture drawn up above the mercury by tilting the tube slightly so that it was sucked up out of the neck by capillarity. The tubes were kept in an oven at 35° to 40° C. during the period of gas formation. Drugs were dissolved in the glucose solution before the latter was put into the tubes. Each drugged tube was accompanied by an undrugged tube as a control, which was filled at the same time and contained the same amount of glucose and yeast as its fellow. The reading of the amount of gas formed in the two tubes was made before the mercury

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[1] Journal of Experimental Medicine, vol. i., No. 4.

[2] Ibid., vol. v. p. 549.

TABLE I.—EFFECT OF DRUGS ON GAS FORMATION BY YEAST IN 2½ PER CENT. GLUCOSE AT 40° C.

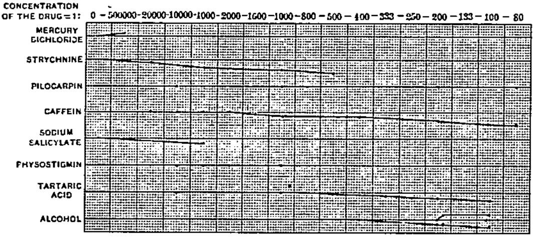
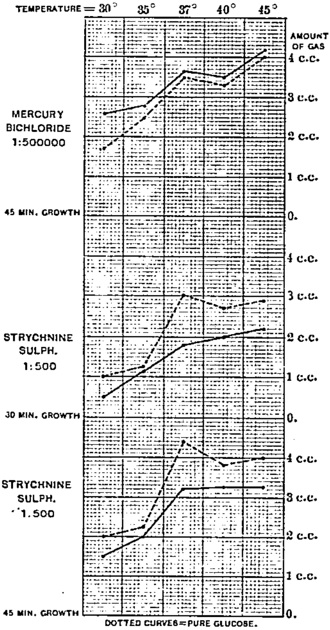


TABLE II.—EFFECT OF TEMPERATURE ON GAS FORMATION.



DOTTED CURVES = PURE GLUCOSE.

had all been forced out of the upright tube. By this means no gas escaped into the air, and the yeast cells were cut off from atmospheric influences.

Results. These are given in the accompanying diagram (Table I.). The strength of the solution of the drug in the glucose-yeast mixture is indicated at the top of the columns. Increase of gas formation is indicated by rise of the action curve above the horizontal line, decrease of gas formation by depression below the line. It will be seen that no reliable stimulant was discovered. Alcohol gave curious results, sometimes having no effect, twice increasing gas formation, but generally decreasing it. The apparent stimulation in two cases may possibly have been due to some error in manipulation. Bichloride of mercury, 1 : 500,000, which is said to have a decided stimulant action on yeast, had but slight action at temperatures above 30° C.

The effect of different temperatures was ascertained in another series of experiments. A temperature intermediate between 35° and 40° C. proved to be the optimum temperature (see dotted curves, Table II.) for fermentation in undrugged tubes. The action of the drugs given in Table I. was the same in quality at 30° C. as at 35° to 40° C., except that bichloride of mercury showed marked stimulant action at 30° C. and very little at higher temperatures. (See Table II.)

All of these drugs were such as either have been reported to stimulate yeast activity or were considered as promising because of known stimulant action on cells of the animal organism.

V. THE ANTAGONISM OF HEAT AND STRYCHNINE ON YEAST.

The search for a reliable stimulant proving fruitless, a study was made of the effect of heat as a physical stimulant, and of the antagonistic action of strychnine in preventing the stimulation by elevation of temperature.

The results of two series of experiments are shown in Table III. It will be noticed that the average percentage of gas production under the influence of strychnine in the two series at 35°, 40°, and 45° C. range from 75 per cent. to 81 per cent. of the glucose for the thirty-minute period of growth, and from 79 per cent. to 86 per cent. for the forty-five-minute period, indicating practically the same degree of strychnine action for all three temperatures.

At 30° and 37° C., however, the depressing action of the strychnine is very much more pronounced for both periods of growth than at any other temperatures (58 to 73 per cent.); therefore we cannot be dealing with a case of pure antagonism, for if the effects of strychnine and heat were strictly antidotal the counteraction should be quantitatively the same at successive temperatures, or should, at least, vary in a constant direction, as it does in the case of time. Table IV. illustrates this point, namely, that the increased amount of gas formed in the forty-five-minute periods as compared with that formed in the corresponding thirty-minute periods would make a fairly smooth curve for both strychnine and glucose.

TABLE III.—EFFECT OF TEMPERATURE ON GAS FORMATION.

	Temperature, amount and percentage of gas.										
	30°		35°		35°-37°		40°		45°		
	C.c.	o/o	C.c.	o/o	C.c.	o/o	C.c.	o/o	C.c.	o/o	
Pure glucose 30 min. growth	1.2	100	1.4	100	2.0	100	2.2	100	2.7	100	1st series.
	0.6	100	1.4	100	3.0	100	2.5	100	2.9	100	2d "
Strychnine 1 : 500 30 min. growth	0.7	58	1.1	78	1.3	65	1.6	72	2.0	74	1st "
	0.4	66	1.2	85	1.9	63	2.0	80	2.2	76	2d "
Pure glucose 45 min. growth	2.1	100	2.3	100	4.0	100	3.4	100	4.0	100	1st series.
	1.4	100	2.7	100	4.5	100	4.0	100	4.0	100	2d "
Strychnine 1 : 500 45 min. growth	1.3	61	2.0	87	2.35	59	3.0	88	3.1	77	1st "
	1.0	71	2.2	81	3.3	73	3.4	85	3.3	82	2d "

TABLE IV.—EFFECT OF TIME ON GAS FORMATION.

	Temperature, amount and percentage of increase.										
	30°		35°		35°-37°		40°		45°		
	C.c.	o/o	C.c.	o/o	C.c.	o/o	C.c.	o/o	C.c.	o/o	
Pure glucose	0.9	76	0.9	57	2.0	100	1.2	54	1.3	48	1st series.
	0.8	133	1.3	92	1.5	50	1.5	60	1.1	38	2d "
Average	0.85	105	1.05	75	1.75	75	1.35	57	1.2	43	
Strychnine 1 : 500	0.6	84	0.9	81	1.0	80	1.4	87	1.1	55	1st series.
	0.6	150	1.0	83	1.4	73	1.4	70	1.1	50	2d "
Average	0.6	117	0.95	82	1.2	77	1.4	78	1.1	53	

In regard to the effect of time, it is to be noted that the increase in the absolute quantity of gas is much more constant in the two series of experiments than is the increase of the percentage of gas.

VI. CONCLUSIONS.

1. Strychnine does not seem to affect the pulse when given simultaneously with alcohol.

2. In some cases (Experiments 1 and 3) strychnine seems to counteract in part the depressing effect of acute alcoholic poisoning on the respiration, and thus prolong life. The apparent exception (Experiment 2) is doubtless explained by the poor physical condition of the cat receiving strychnine and by the small dose.

3. Strychnine does not seem to interfere materially with the narcosis from acute poisoning with alcohol, but, apparently, does delay the onset of paralytic symptoms.

4. In subacute alcoholic poisoning (Experiment 4) strychnine seems to lessen the narcosis and paresis in the earliest stages, but in the later stages to increase the depression. However, a general conclusion is hardly justified, since only one control experiment was made.

5. Although in no case was the strychnine competent to completely remove the effects of the large doses of alcohol which were employed, yet it may be considered probable that appropriate doses of strychnine (fairly strong therapeutic doses) would prove useful in the treatment of poisoning from even lethal doses of alcohol.

6. No action on the nerve cells by either alcohol or strychnine was demonstrable histologically.

7. Many drugs depress the activity of yeast cells, but no reliable stimulant was found; therefore the antagonism of drugs in their action on these cells could not be studied.

8. Heat was found to be a reliable stimulant up to 45° C., but strychnine as an antidote to heat did not give uniform results at the successive temperatures, so that the antagonism is not a simple one.

BLOOD CHANGES IN DEMENTIA PARALYTICA.

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THE blood of patients suffering from dementia paralytica has been the subject of microscopic study by many observers during the past fifty years, but none have made regular and systematic examinations extending over a considerable portion of the course of the disease. Believing that such a study, so conducted as to eliminate all known physiological changes, might throw further light upon the nature of this